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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/431,533	11/03/89	MORTON	D P318462

EXAMINER

HM22/0816

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ART UNIT 1642 | PAPER NUMBER 68

DATE MAILED: 08/16/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 08/03/98.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 19, 62-66, 69, 70, 72-79 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 19, 62-66, 69, 70, 72-79 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 67, 68, and 71.

Claims 19, 62-66, 69-70, and 72-79 are being examined.

The following rejections are withdrawn: 1) Rejection of claim 62 under 35 USC 102, in view of applicant's amendment, 2) Rejection of claims 19, 62-79 under 35 USC 103, in favor of a new 103 rejection, to incorporate a new reference.

REJECTION UNDER 35 USC 101, NEW REJECTION

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19, 62-66, 69-70, 72-79 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-17, 48-60 of copending application Serial No. 08/462,570. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims 19, 62-66, 69-70, 72-79 in the present application are drawn to an antigen composition comprising UTAA, and a method for inducing or enhancing the production of antibodies reactive to UTAA comprising administering UTAA, whereas the claims 14-17, 48-60 are drawn to an antigen composition comprising UTAA, GM-2, GD-2, fetal antigen, and MTAA, and a mixture of tumor cells, and a method for inducing or enhancing the production of antibodies reactive to UTAA comprising administering UTAA, and at least one tumor associated antigen selected from the group consisting of GM-2, GD-2, fetal antigen, or MTAA. The claims 19, 62-66, 69-70, 72-79 in the present application and 14-17, 48-60 in the application SN 08/462,570 are both drawn to the same antigen UTAA, and the same method of producing antibodies reactive to UTAA, and accordingly, are obvious variants.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Therefore, the inventions as claimed are co-extensive.

REJECTION UNDER 35 USC 103, NEW REJECTION

Claims 19, 62-66, 69-70, and 72-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Euhus et al., *supra*, in view of Exley, AR, 1990, Cytokine, 2(5): 353-6, Rote, NS et al., 1980, J Surgical Research, 29: 18-22, or Finck SJ et al, 1982, J Surgical Oncology, 21: 81-86, Pharmacia Fine Chemicals, Gel filtration, Theory and practice, 1980, pages 4, 14, 26-27, Pharmacia fine Chemicals, Ion exchange chromatography, Principles and methods, 1980, pages 3-7, 43-47, Ljungquist, S, 1977, JBC, 252(9): 2808-2814, and Goldenberg, 1982, US 4,348,376.

Claims 19, 62-66, 69-70, and 72-79 are drawn to an isolated Urinary Tumor Associated Antigen (UTAA) subunit, which after reduction by beta-mercaptoethanol and separation by SDS-polyacrylamide gel electrophoresis (SDS-PAGE), exhibits a molecular weight of about 90 to 100 kD. Said UTAA is purified at least about 100-fold, or 105-fold over UTAA found in urine, and is present as at least about 0.6% of total protein in the original composition. Said UTAA is about 95% or 99.5% free of immunoglobulin. Claims 19, 62-66, 69-70, and 72-79 are also drawn to a pharmaceutical composition comprising said purified UTAA, and a pharmaceutical buffer, wherein said UTAA is present as at least about 0.63 ug/ml, or 1.4 ug/ml, or 36 ug/ml, or 40 ug/ml, or 100 ug/ml, or 200 ug/ml of buffer. Claims 19, 62-66, 69-70, and 72-79 are further

drawn to a method for inducing or enhancing in a subject the production of antibodies reactive with UTAA, comprising administering said purified UTAA. The observed enhancement of antibody production is about 2- to 5-fold.

Euhus et al. teach the isolation of urinary tumor asssociated antigen (U-TAA) from sera of melanoma patients. Euhus et al. also teach that because said antigen was detected in the urine of melanoma patients, using autologous and allogeneic antibody in ELISA, it was termed urinary tumor asssociated antigen . A monoclonal antibody to U-TAA is developed, and used in ELISA to detect U-TAA. Said U-TAA is isolated by dye ligand, and gel filtration chromatography, and DEAE anion exchange chromatography or 4.5% polyethylene glycol precipitation. The free U-TAA in serum has a molecular mass of 620 kD, which is separated into four bands in SDS-PAGE; two of which, 142 kD and 111 kD, correspond to those present in U-TAA in urine. The isolated U-TAA is free of IgG and IgM. Euhus et al. further teach that pure U-TAA antigen will provide valuable reagents for the immunoprognosis of human melanoma.

Euhus et al. do not teach that UTAA is purified at least about 100-fold, or 105-fold over UTAA found in urine, and is present as at least about 0.6% of total protein in the original composition. Euhus et al. do not teach that said UTAA is about 95% or 99.5% free of immunoglobulin. Euhus et al. do not teach a pharmaceutical composition, wherein said UTAA is present as at least about 0.63 ug/ml, or 1.4 ug/ml, or 36 ug/ml, or 40 ug/ml, or 100 ug/ml, or 200 ug/ml of buffer. Euhus et al. do not teach a method for inducing or enhancing in a subject the

production of antibodies reactive with UTAA, comprising administering said purified UTAA, wherein the observed enhancement of antibody production is about 2- to 5-fold.

Exley et al teach how to perform enzyme-linked immunosorbent assay or ELISA.

Rote et al. teach tumor-associated antigens detected by autologus sera in urine of patients with solids neoplasms, using complement fixation assay. Unlike other tumor-related urinary antigens, the antigens taught by Rote et al induce a complement fixing antibody in the host, are heat stable at 100^0 C for 60 min. Said antigens are comprised of molecules of about $1x\ 10^6$ daltons, which could be dissociated into smaller subunits by treatment with 6 M urea.

Finck et al teach tumor-associated antigens found in urine of patient with colon carcinoma. Said antigen could be detected with complement fixation assay, using autologous serum as the antibody source. Said antigen has a molecular weight of >100,000 dalton, and is heat stable at 100^0 C (p.85).

Pharmacia Fine Chemicals teach how to purify proteins using gel filtration and ion exchange chromatography. Pharmacia teaches that "the separation of proteins in gel filtration depends on the different abilities of the various sample molecules to enter pores which contain the stationary phase. Very large molecules which never enter the stationary phase, move through the chromatographic bed fastest" Smaller molecules are eluted in order of decreasing molecular size" (Gel filtration, page 4). The eluent is just a simple buffer solution, as shown in one example on figure 6, page 14 (Gel filtration). Furthermore, molecular weight standards are routinely used for calibrating the gel filtration column (Gel filtration, pages 26-27). It is well known in the art that

molecular weight standards could be easily tagged with dye ligands for color detection on the column. Pharmacia also teaches methods of elution of proteins from ion exchange columns, including DEAE columns, using a continuous NaCL gradient (Ion exchange chromatography, pages 3-7, 43-47). Peaks of different proteins are separated by said continuous gradient elution, and thus could be detected.

Ljunquist teaches the purification of endonuclease IV by 3000-fold, using a combination of ammonium sulfate, gel filtration on Sephadex G-75, heat treatment, and DNA-cellulose.

US 4,348,376 teaches production of antibodies to the tumor antigen CEA, and the use of said antibodies for tumor localization and therapy.

The art establishes that it was possible at the time the invention was made to isolate UTAA from sera of melanoma patients. Said UTAA is termed urinary tumor associated antigen because it is detected in urine of melanoma patients. A subunit of said UTAA from sera is 111 kD in SDS-PAGE, corresponding those present in UTAA in urine. Although 111 kD is not 90 to 100 kD, it is well known in the art that molecular weight determination by SDS-PAGE, at high molecular weight range, is not very accurate, and could easily vary by 10%. As also shown by applicant's own data, the molecular weight of the claimed UTAA varies by about 10%. Thus the 111 kD UTAA taught by Euhus et al. could have a similar molecular weight as the claimed UTAA. The art also teaches the protocols for isolating UTAA, i.e. by gel filtration, and DEAE anion exchange columns. Although the abstract by Euhus et al does not describe in detail how to isolate UTAA using gel filtration, and DEAE anion exchange columns, it is a routine protocol in

the art, as shown in the handbooks Pharmacia, or Ljungquist. In other words, proteins of different sizes are separated by gel filtration, using a simple buffer solution; and different proteins are separated by a DEAE column, eluted as different protein peaks, using a continuous salt gradient elution. The art further teaches how to detect UTAA, i.e. either by ELISA, or by complement fixation test, using autologous or allogeneic sera of melanoma patients. Although the abstract by Euhus et al does not describe in detail how to perform ELISA, ELISA is a routine protocol in the art, as shown by Exley et al. Thus the eluted peaks from gel filtration or DEAE column could be detected by either ELISA or by complement fixation test, using autologous or allogeneic sera of melanoma patients.

Therefore, it would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to purify UTAA from urine samples of melanoma patients, using the purification methods taught by Euhus et al, Pharmacia, and Ljungquist, and the detection methods taught by Exley et al, Rote et al, and Finck et al. Although isolated from sera of melanoma patients, the isolated UTAA, as taught by Euhus et al, is the same as the claimed UTAA, which is isolated from urine of melanoma patients, because UTAA is originally found in urine of melanoma patients, and because the molecular weight (111 kD) of a subunit of UTAA taught by Euhus et al. is not significantly different from that of the claimed UTAA, having a molecular weight from about 90 kD to about 100 kD. Furthermore, the isolated UTAA taught by Euhus et al is free of IgG and IgM, and thus is at least 95% or 99.5% free of immunoglobulin. Although Euhus et al. do not specifically teach the degree of purification of UTAA, such degree

of purification is expected, given similar protocols used by Euhus et al. and applicant. Once UTAA is isolated, it would have been obvious to dilute it or to concentrate it to various concentrations in a buffer.

It would have been obvious to use UTAA for inducing or enhancing the production of antibodies reactive to UTAA, because Euhus et al suggest the use of the isolated UTAA for the immunoprognosis of human melanoma, and because it is well known in the art that tumor antigens are used for the production of antibodies, and antibodies to tumor are used for treating tumors (see for example, US 4,348,376). Furthermore, administering the same antigen UTAA is expected to give similar 2- to 5-fold enhancement in the production of antibodies reactive to UTAA, because the specification does not disclose any specific method of production of antibodies which is different from routine methods of production of any antibody known in the art.

One of ordinary skill in the art would have been motivated to isolate UTAA from urine of melanoma patients, and to use said isolated UTAA for inducing or enhancing the production of antibodies reactive to UTAA, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to isolate UTAA from urine of melanoma patients, and to use said isolated UTAA for inducing or enhancing the production of antibodies reactive to UTAA for the immunoprognosis of melanoma.

Claims 73-79, drawn to a pharmaceutical composition, read on UTAA in a carrier, i.e. water. The language pharmaceutical composition is not given any patentable weight in applying prior art.

ANSWERS TO APPLICANT'S ARGUMENTS.

Applicant argues as follows:

1) The prior art fails to teach which fraction contained UTAA, or how one could indentify UTAA from any other protein using any readily obtainable, well characterized antibodies.

2) The secondary references do not provide any indication as to how these procedures should be applied to the present invention.

3) Applicant submits a new declaration by Dr. Shively. Dr. Shively recites that based on the comparison of the abstract by Euhus et al, and subsequent articles by Euhus et al, Int. J. Cancer, 45: 1065-1070, and Euhus et al, 1990, Cancer Immunol. Immunother., 32: 214-220, the antigen as described in the abstract was not purified to homogeneity, nor characterized sufficiently to allow even an expert to positively identify the same antigen. In other words, insufficient information was given in the abstract to identify serum that are free of immune complexes for use in the purification, or to modify the isolation procedure to successfully isolate the antigen under these circumstances. Therefore, the antigen as described in the abstract was not purified to homogeneity. Furthermore, the abstract by Euhus et al does not provide sufficient details to reproduce the purification and identification of UTAA.

Applicant's arguments set forth in paper No. 62 have been considered but are not deemed to be persuasive for the following reasons:

1) One of ordinary skill could identify UTAA fractionnated from the chromatographic column, using ELISA, a method well known in the art, as taught by Euhus et al, and Exley et al, and by complement fixation, as taught by Rote et al, and Finck et al. Complement fixation is used because unlike other tumor-related urinary antigen, UTAA induces a complement fixing antibody. The antibody source for said ELISA and complement fixation is from autologous and allogeneic antibody from serum of Stage II and III melanoma patients, as taught by Euhus et al, Rote et al, and Finck et al.

2) The secondary references are provided to teach the details of the common purification and characterization methods taught in the abstract by Euhus et al. With the protocols taught by these references, it is well within the ability of one of ordinary skill in the art to apply said protocols for the purification and characterization of UTAA.

3) The declaration by Dr. Shively could not be entered because it was not signed by Dr. Shively. Furthermore, the articles recited by Dr. Shively could not be considered because they were not submitted with the declartion. Moreover, the declaration is not convincing, unless applicant submits actual data comparing the degree of purification using the methods by the abstract by Euhus et al, and by the claimed invention. In addition, nowhere in the specification does applicant disclose the identification of serum that are free of immune complexes for use in the purification, or the modification of the isolation procedure to successfully isolate the antigen under these circumstances. The burden is upon applicant to provide evidence that such method, as disclosed in the declaration by Dr Shively, was actually used by applicant. Concerning insufficient

details in Euhus abstract, the secondary references are provided to teach the details of the common purification and characterization methods taught in the abstract by Euhus et al, *supra*.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 7:00am to 3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2297. The fax phone number for this Group is (703) 308-4227.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**lila.feisee@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless **the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122.** This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

July 24, 1998

LILA FEISEE
SUPERVISORY PATENT EXAMINER